

NRITLD Protocol for the Management of Outpatient Cases of COVID-19

Mitra Rezaei ¹, Hamidreza Jamaati ², Payam Tabarsi ¹, Afshin Moniri ¹, Majid Marjani ¹, and Ali Akbar Velayati ¹

¹ Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, ² Chronic Respiratory Disease Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Correspondence to: Marjani M

Address: Clinical Tuberculosis and Epidemiology Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email address: marjani@sbm.ac.ir

Despite the fact that about two years have passed since the onset of the COVID-19 pandemic, there is still no curative treatment for the disease. Most cases of COVID-19 have mild or moderate illness and do not require hospitalization.

This guideline released by the National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshvari Hospital COVID-19 Expert Group to provide a treatment guide for outpatient management of COVID-19.

Key words: COVID-19; SARS-CoV-2; Outpatient; Remdesivir

INTRODUCTION

The first case of coronavirus disease 2019 (COVID-19) caused by a new strain of coronavirus, namely severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was reported from China in December 2019 shortly led to a global health problem and pandemic (1). By August, 2021, the total number of 211,288,358 laboratory-confirmed cases of COVID-19 were reported, with 4,422,666 deaths worldwide (2). Iran reported its first confirmed cases of COVID-19 on February 19, 2020, in Qom (Qom province, Iran) (3), and by August, 2021, 4,833,135 confirmed cases and 104,716 deaths were reported from Iran (4).

To date, there has been no proven curative treatment for this virus supported by any randomized clinical trials (5). However, various antiviral and anti-inflammatory drugs have been studied, and different and sometimes contradictory results have been reported.

Scope of NRITLD Protocol and Ethical Issues

This guidance was released by the National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshvari hospital COVID-19 expert group, the second one in this series (6), and might help the clinicians caring for outpatient cases of COVID-19. Care of severe and inpatient cases and interventions for infection control are beyond the scope of this paper.

Due to the emerging aspect and evolving knowledge of COVID-19, any recommendation might change in the future. Therefore, clinicians should update their information in short periods. On the other hand, adherence to national and local guidelines is mandatory, and the prescription of any drug out of national protocols should be made just under approved clinical trials with ethical committee permissions and informed consent from patients.

Classification of Severity

In the NRITLD guideline, the severity of respiratory problems in COVID-19 is classified as follows: (7)

Mild: Symptomatic patients without pulmonary infiltration

Moderate: Patients with pulmonary infiltration less than 50% of the lung field and at rest oxygen saturation (SpO_2) \geq 94% with ambient air

Severe: Patients with one of the criteria, including a respiratory rate of \geq 30 breaths/minute, $\text{SpO}_2 \leq$ 93% with ambient air, or pulmonary infiltrates in more than 50% of the lung field, and not in a critical state

Critical: Patient requiring critical care in an intensive care unit, with high flow oxygen, noninvasive ventilation, mechanical ventilation, and acute respiratory syndrome distress or shock.

Indications for Virologic Assay and Other Laboratory Tests

In the presence of any suspicious symptoms (e.g., fever, myalgia, arthralgia, cough, and dyspnea) or a history of contact with an affected individual, a reverse transcription-polymerase chain reaction (RT-PCR) test should be requested. A nasopharyngeal swab is a preferred method to obtain a specimen for testing (8).

Clinicians should consider that a single negative RT-PCR is insufficient to exclude COVID-19, especially if clinical suspicion is high. Clinicians should consider test repetition and finally might rely on compatible symptoms, exposure history, and typical computed tomography (CT) imaging features for COVID-19 diagnosis (9). Negative RT-PCR test does not change the therapeutic management or prevention measures (i.e., isolation).

In the case of mild illness and SpO_2^1 of 94 or higher, other laboratory tests, such as C-reactive protein (CRP), complete blood count (CBC), and ferritin, should be avoided. Serological testing (e.g., immunoglobulin M and Immunoglobulin G) has no place except in special cases (10).

Indications for Imaging Study

Any individual suspected of COVID-19 with any of the following conditions should undergo a chest imaging examination:

- Feeling shortness of breath
- Arterial SpO_2 of 93 or less
- Fever persistence for 5 days or more
- Those at higher risk for disease progression:
 - Underlying heart or lung disease, diabetes mellitus, hypertension, body mass index of >30 , sickle cell disease, transplant recipients, chronic renal failure, and individuals over 60 years of age.

The most sensitive modality is a lung CT scan (11), and it is recommended to undergo a low-dose spiral lung CT scan as the preferred examination. In symptomatic immunocompromised individuals, especially if they are hypoxic or febrile, a CT scan of the lungs should be performed, and a normal chest X-ray should not be relied upon.

The CT scans in mild cases (SpO_2 of 94 and above without shortness of breath) should be avoided. Additionally, the routine use of CT scan as a screening test among asymptomatic cases is highly deferred (12, 13).

Indications for Outpatient Remdesivir Therapy

- In the case of pulmonary involvement below 50%, if SpO_2 is \geq 90 and \leq 93

OR

- In the case of lung involvement below 50%, even if SpO_2 is above 93; however, there is a very high suspicion of hypoxia in the following days² (7, 10, 14, 15).

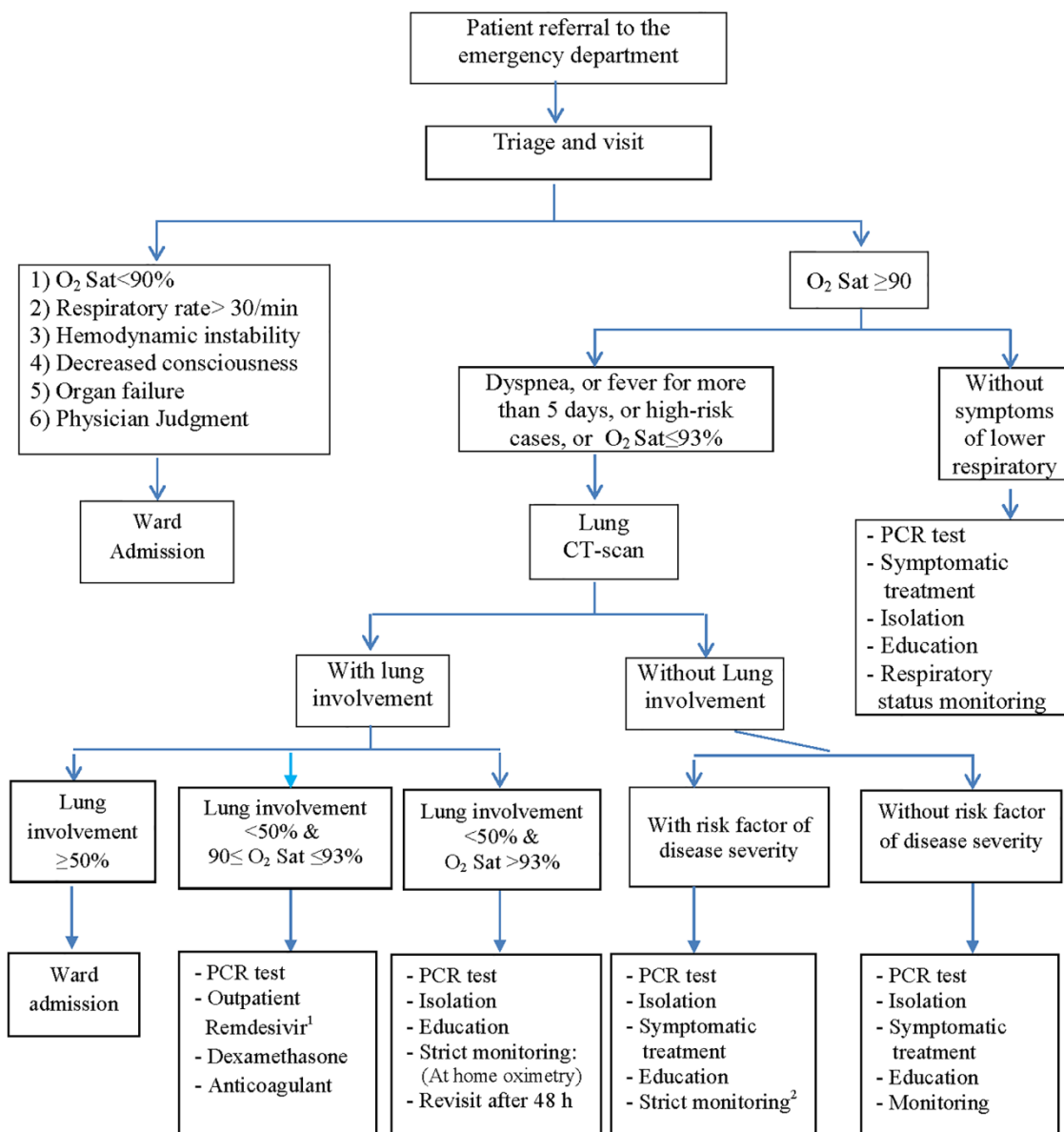
Indications for Admission

- Tachypnea higher than 30 per minute
- $\text{SpO}_2 < 90$
- Loss of consciousness
- Intolerance to food
- Hemodynamic instability (shock state)
- Failure of function of one or more organs
- Special cases (e.g., a non-critical but high-risk patient who is alone at home)

Figure 1 shows a flowchart for the management of outpatient cases of COVID-19.

¹ In this instruction, oxygen saturation refers to SpO_2 at rest, sitting, and room air.

² In the case of involvement of less than 50% of the lungs' field, even if the general condition is good, the patient should be revisited after 48 h.



1. We recommend against the start of Remdesivir after the 10th day of the onset of symptoms.
 2. Re-visit after 72 hours.

Figure 1. Flowchart for the management of outpatient cases of COVID-19

Management of Outpatient Cases

Non-severe cases (SpO₂ above 93) do not require temporary or permanent hospitalization; nevertheless, it should be recommended that the patient returns if the symptoms worsen or the fever persists above 4 days. Patient education, especially about the signs of deterioration, is necessary. Pulse oximetry should be educated and performed at home for high-risk individuals.

In those who are not in the high-risk group, only conservative treatment should be prescribed. Some suggestions are as follows:

- For fever control: Acetaminophen
- For skeletal and muscle pains: Naproxen or other nonsteroidal anti-inflammatory drugs
- For cough suppression: Diphenhydramine compound, dextromethorphan, and/or bromhexine

- For epigastric pain control: Famotidine
- Antiviral therapy may be considered in those at higher risk of disease progression. However, there is no suitable choice in the current situation and based on the drugs available in Iran.

Not Recommended for Outpatients: (7, 10, 16)

- Remdesivir injection at home is not recommended.
- Kaletra® (lopinavir/ritonavir) is not recommended.
- Hydroxychloroquine is not recommended.
- Colchicine is not recommended.
- Prednisolone and dexamethasone are not recommended in cases without hypoxia.
- In the absence of evidence of secondary bacterial infection, antibiotics (e.g., azithromycin and levofloxacin) are not recommended.
- Sofosbuvir/daclatasvir is not recommended.
- There is no evidence that Ivermectin is effective.
- Aspirin and anticoagulants are not recommended without other indications.
- Interferon beta is not recommended, especially in severe cases or in the second week of the illness.
- Prescribing vitamins (e.g., C and D), zinc, and other supplements have no effect.

Protocol of Outpatient Remdesivir Therapy

We recommend against the start of Remdesivir after the 10th day of the onset of symptoms.

For candidates of outpatient remdesivir therapy, the following combination is recommended:

- 1) Dexamethasone 8 mg daily (the preferred dose is 6 mg; however, the available form in Iran is 8 mg ampules.) (2, 7, 10, 17)
- 2) Remdesivir loading dose of 200 mg and then 100 mg per day to complete 5 days (7, 10) as a slow infusion.
- 3) Prescription of a prophylactic anticoagulant, especially if the patient's activity is severely restricted. The best option is low-molecular-weight heparins, such as enoxaparin. (40 mg subcutaneous enoxaparin or 7500 units subcutaneous heparin or equivalent daily)

Considerations About Outpatient Remdesivir Therapy

The site of remdesivir infusion should be equipped with oxygen and resuscitation facilities. During the infusion, the patient should be monitored for bradycardia and other reactions to the drug. As remdesivir might cause severe bradycardia, atropine should be available. In addition, if needed, a physician should be available, or referring to a specialized center might be possible.

In the first and third days and preferably the last day of the remdesivir infusion, laboratory tests, including CBC, CRP, blood urea nitrogen, creatinine, and liver function tests, should be performed. Furthermore, if possible, inflammatory factors, such as lactate dehydrogenase, ferritin, and coagulation factors, should be checked on the first day.

General condition and SpO₂ should be checked, and a daily visit by a physician is necessary. Moreover, if the patient's condition worsens during this period or blood SpO₂ drops to the threshold of hospitalization, the patient should be transferred to the hospital ward. Remdesivir therapy might need to be discontinued if the alanine transaminase (ALT) level increases (7) to more than five times the upper limit of normal (ULN) or if there was an increase in ALT level to more than three times the ULN consistent with the signs or symptoms of liver inflammation (i.e., nausea, vomiting, weakness, or anorexia).

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020;382(8):727-733.
2. World Health Organization. COVID-19 weekly epidemiological update, edition 54, 2021. <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---24-august-2021> Accessed August 27, 2021. 2020.
3. Olfatifar M, Hourri H, Shojaee S, Pourhoseingholi MA, Alali WQ, Busani L, et al. The required confronting approaches

- efficacy and time to control COVID-19 outbreak in Iran. *Archives of Clinical Infectious Diseases* 2020;15:4.
4. The current COVID-19 situation. Iran profile. Accessed August 27, 2021. <https://www.who.int/countries/irn/>
 5. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med* 2020;383(25):2451-2460.
 6. Marjani M, Tabarsi P, Moniri A, Hashemian SM, Nadji SA, Abtahian Z, et al. NRITLD Protocol for the Management of Patients with COVID-19 Admitted to Hospitals. *Tanaffos* 2020;19(2):91-99.
 7. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19treatmentguidelines.nih.gov/>. Accessed August 4, 2021.
 8. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020;323(18):1843-4.
 9. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020;382(18):1708-1720.
 10. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. *Clinical Infectious Diseases*. 2020. Available at <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>. Accessed August 27, 2021.
 11. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020;296(2):E115-E117.
 12. American College of Radiology. ACR recommendations for the use of chest radiography and computed tomography (CT) for suspected COVID-19 infection. 2020 (<https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection>).
 13. Use of chest imaging in COVID-19: a rapid advice guide. Geneva: World Health Organization; 2020 (WHO/2019-nCoV/Clinical/Radiology_imaging/2020.1). Licence: CC BY-NC-SA 3.0 IGO.
 14. Benfield T, Bodilsen J, Brieghel C, Harboe ZB, Helleberg M, Holm C, et al. Improved survival among hospitalized patients with COVID-19 treated with remdesivir and dexamethasone. A nationwide population-based cohort study. *Clin Infect Dis* 2021:ciab536.
 15. Wong CKH, Lau KTK, Au ICH, Xiong X, Chung MSH, Lau EHY, et al. Optimal timing of remdesivir initiation in hospitalized COVID-19 patients administered with dexamethasone. *Clin Infect Dis* 2021:ciab728.
 16. World Health Organization. COVID-19 Clinical management: living guidance. 2021. WHO/2019-nCoV/clinical/2021.1. Available at: <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1> last accessed: August 27, 2021.
 17. Dunay MA, McClain SL, Holloway RL, Norris SLW, Bendixsen Randall T, Mohr CE, et al. Pre-Hospital Administration of Remdesivir during a SARS-CoV-2 Outbreak in a Skilled Nursing Facility. *Clin Infect Dis* 2021:ciab715.